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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,217	02/21/2002	Gregory R. Mundy	A061CIP2	5114

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,217	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-98,100 and 101* is/are pending in the application.

4a) Of the above claim(s) *90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-89, 91-98, 100 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/14/06 has been entered.

2. Claims 86-98 and 100-101 are pending.

3. Claim 90 stands withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 86-89, 91-98, 100 and 101 are under consideration in the instant application as they read on a method of treating multiple myeloma with a composition comprising an anti-VLA-4 antibody and the species of chemotherapeutic agent melphalan.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 86-89, 91-98, 100 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,692,742 (listed previous on PTO-892) in view of Lokhorst et al (Blood 84:2269-2277, 1994) and Masellis-Smith et al (IDS Ref No. A1).

The US `742 patent teaches teach and claims a method for treating multiple myeloma patients comprising administering anti-IL-6 antibodies (a reshaped human PM-1 antibody with melphalan to a subject in need of such treatment) (see patented claim 1in particular), wherein the reshaped human PM-1 antibody is the antibody hPM-1(see patented claim 2 in particular). Anti-IL-6 receptor antibodies act via binding to IL-6 receptor, block the binding of IL-6 to IL-6 receptor,

and thereby inhibit signal transmission of IL-6, and therefore are antibodies which inhibit the biological activity of IL-6. The `742 patent further teaches that the effective dosage of anti-IL-6 receptor antibody is chosen from the range of 0.001 mg to 1000 mg per kg of body weight per day. Preferably, the dosage is selected from the range of 0.01 to 50 mg per body weight (see col., 15, line 24-28 in particular). The `742 patent teaches that monoclonal antibodies (col., 8, line 2), chimeric antibody and humanized antibody can be used for the purpose of lowering xenogenic antigenicity against humans (see co., 9, lines 1-6 in particular). Further, the `742 patent teaches that human antibody having the activity of binding to and neutralizing IL-6 receptor (col., 7, lines 33-41 in particular). In addition, the `742 patent teaches that fragments of antibody such as Fab, F(ab')2, Fv or single-chain Fv (scFv) (see col., 10, lines 33-35 in particular). Furthermore, the ` 742 patent teaches compositions comprising a nitrogen mustard anticancer agent and anti-IL-6 receptor antibody (see col., 15, lines 13-15 in particular). Finally, the `742 patent has found that the combination of a nitrogen mustard anticancer agent (such as melphalan), a conventionally known anticancer agent, and anti-IL-6 receptor antibody has a synergistic effect, i.e. it is more effective than the sole use of the nitrogen mustard anticancer agent or the sole use of anti-IL-6 receptor antibody for treatment of myeloma (see col. 1, line 66 to col., 2, line 6, Fig. 9 and Examples 1 and 2 in particular).

The reference teaching differs from the claimed invention by not expressly disclosing to employ an antibody anti-VLA-4 antibody or antigen binding fragment thereof in claims 86, 100 and 101.

Lokhorst *et al* teach monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Furthermore, Lokhorst *et al* teach that the intimate cell-cell contact is a prerequisite for IL-6 induction and the physical separation of plasma cells and LTBMC by mechanical means such as monoclonal antibodies to VLA-4 which is involved in the adhesion process, inhibit the induction of IL-6 production by LTBMC (entire document and abstract page 2269, and page 2276, left column 2nd paragraph in particular).

Masellis-Smith *et al* teach function-blocking monoclonal antibodies such as mAbs against very late antigen 4 that inhibit the CD19+ multiple myelom blood B cell interaction with BM fibroblasts. Furthermore, Masellis-Smith *et al* teach that the alpha4beta7 ligand is mediated MM blood B cell adhesion (see the entire document and abstract page 930 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-IL-6 receptor antibody taught by the `742 patent with the antibody that specifically binds VLA-4 antibody taught by Lokhorst *et al.*, and Masellis-Smith *et al* in a method of treating multiple myeloma (MM) taught by the `742 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to to do so because antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst *et al* and because antibodies against alpha4

integrin inhibit the adhesion of alpha4beta7 integrin of B cells from MM patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM.

Claim 97 is included because the referenced anti-VLA-4 antibodies are B epitope because anti-alpha4 antibody is an antibody which can bind VLA-4 at a site involved in ligand recognition and block VCAM-1 binding. Thus the referenced anti-VLA-4 antibody belongs by definition to the B epitope-specific group. Therefore, being B-epitope-specific is considered an inherent property of the referenced antibody.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 9/14/06, have been fully considered, but have not been found convincing.

Applicant disagrees with in two points: i) that one of ordinary skill in the art would have been motivated to substitute the anti-IL-6 antibodies of Van Zaanen with anti-α4 antibodies and ii) that one of ordinary skill in the art would have been motivated to combine anti-α4 antibodies with a chemotherapeutic agent such as melphalan for the treatment of MM.

The Examiner will only address the 1st point because the 2nd point is moot in view of the new reference U.S. Pat. No. 6,692,742.

Applicant points to Dr. Mundy declaration under 1.132 to question the relevance of the Examiner's use of the antibody interchangeability in the 103(a) rejection that is the substitution of anti-α4 antibody for anti-IL-6 antibody. Applicant submits that the art did not teach that the anti-IL-6 antibodies could be used to treat MM. Applicant points to Bataille *et al* to point that anti-Il-6 antibodies were not effective at treating MM in patients with advanced MM.

Regarding the applicant's submission that the art did not teach the anti-IL-6 antibodies can be used to treat MM. The Examiner notes that the `742 patent claims and teach the use of anti-IL-6 receptor antibodies with melphalan to treat MM. The claims are presumed enabled. Regarding Bataille et al, the examiner notes that while the `742 patent is presumed enabled for both the advance MM as well as un-advance MM, the instant application claims do not exclude advance MM in the method of treating MM. The instant claims read on all types of MM. Further, the claims are directed to methods of treating, not methods of curing. Accordingly, any improvement in either Bataille et al or van Zaanen et al is considered a treatment of MM.

Applicant argues that Masellis-Smith also found that anti-VCAM-1 and anti-fibronectin antibodies did not affect B cell adhesion and accordingly concluded that the anti-α4 antibodies HP2/1 inhibits B cell adhesion via a novel ligand.

However, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious.

Regarding Lokhorst, Applicant points to Dr. Mundy's declaration to question the logic of substitution anti-α4 antibodies with the IL-6 antibodies for treatment of MM.

The declaration by Dr. Mundy's under 37 CFR 1.132 filed 9/14/06 is insufficient to overcome the rejection of based upon 35 U.S.C. § 103(a).

The declaration on ¶4 states that the art did not teach the anti-IL-6 antibodies could be used to treat MM. The declaration points to Bataille et al reference who show that anti-IL-6 antibodies were not effective at treating MM. Further, the declaration contends that Van Zaanen results is at best a phase I dose-escalating study which show that anti-IL-6 antibodies are not toxic.

However, the rejection substitutes Van Zaanen reference with the U.S. Patent 6,692,742 that by statute is presumed to be valid and claims are presumed to be enabled to treat advanced and un advanced MM. Further, the instant claims are drawn to methods of treating not curing MM. As long as there are some improvement in the MM patient in both Bataille et al or Van Zaanen, then the claims read on the method.

The Declaration on ¶5, states that in view of the fact that anti-VLA-4 antibodies decrease tumor burden in mouse models of myeloma bone disease, and that anti-IL-6 is not effective as a treatment for myelma, one of the ordinary skill in the art would conclude that although anti-VLA4 antibodies can decrease IL-6 levels (at least in vitro), this does not appear to be relevant to the anti-tumor effect of the anti-VLA-4 antibodies (emphasis added by the declaration). The Declaration further states that anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6 (emphasis added by the Declaration). Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells dies. The declaration further states that there may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4, but this is a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells dies.

Again, the U.S. Patent 6,692,742 by statute is presumed to be valid and claims are presumed to be enabled to treat all types of MM. The idea of combining the references flows logically from the `742 patent teachings methods of treating MM with anti-IL-6 receptor antibodies and melphalan, antibodies which inhibit the biological activity of IL-6, to the Lokhorst et al teachings

that monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Given that antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst et al the ordinary skilled in the art would be motivated to substitute the anti-IL6 receptor antibody taught by the `742 patent with the anti-VLA-4 antibodies taught by Lokhorst et al. Further, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed the mechanism by which a particular anti-VLA-4 antibodies and a melphalan alleviates symptoms of MM does not appear to distinguish the prior art teaching the same methods to achieve the same end result.

The declaration on ¶6-8, regarding the combination therapy is considered irrelevant in view of the `742 patent teachings of treating MM with anti-IL-6 antibodies and melphalan.

On the top of page 11 of the remarks, regarding the unexpected results, Applicant argues that anti-IL-6 receptor antibody will disrupt a multitude of pathways, as this receptor interacts with two classes of ligands called gp130 ligand and gp80 ligands (emphasis added by Applicant). Accordingly, Applicant concludes evidence that a combination of anti-IL-6 receptor antibodies and melphalan can treat MM, one of skill in the art would not conclude that an anti-VLA-4 antibody, which disrupts a very different interaction) in combination with a chemotherapeutic agent would also be effective for the treatment of MM.

However, combination therapy, in general, supports appropriate level dosing in that it allows the application of doses of individual agents lower than those that elicit the unwanted side effects that may occur at higher dose levels. In the case of combining agents that work toward a broadly defined common benefit but which operate through different mechanisms of action, synergistic therapeutic effects may occur. Synergistic effects, by their nature, are not commonly predictable, based solely on an understanding of the mechanisms of the combined individual agents, respectively.

7. The declaration filed under 37 CFR1.132 by Dr. Blake Pepinsky on 10/28/05, referred to as Exhibit B, filed in the grandchild U.S. application, 09/805,840 has obviated the rejection under 35 U.S.C 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata et al and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969. Said declaration states that anti-α4 integrin antibodies have a different specificity than oMePUPA-V and does not act on α4β7 integrin. Further said declaration states that oMePUPA-V binds at the ligand binding site and therefore may act as an agonist. The declaration concludes that oMePUPA-V is not interchangeable with an anti-α4 integrin antibody.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 21, 2006

Maher Haddad

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